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The Effect of Age on Clinical Outcomes and Health Status

BARI 2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes)

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Objectives The purpose of this study was to determine the extent to which effectiveness of cardiac and diabetes treatment strategies varies by patient age.

Background The impact of age on the effectiveness of revascularization and hyperglycemia treatments has not been thoroughly investigated.

Methods In the BARI 2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes) trial, 2,368 patients with documented stable heart disease and type 2 diabetes were randomized to receive prompt revascularization versus initial medical therapy with deferred revascularization and insulin sensitization versus insulin provision for hyperglycemia treatment. Patients were followed for an average of 5.3 years. Cox regression and mixed models were used to investigate the effect of age and randomized treatment assignment on clinical and health status outcomes.

Results The effect of prompt revascularization versus medical therapy did not differ by age for death (interaction $p = 0.99$), major cardiovascular events (interaction $p = 0.081$), angina (interaction $p = 0.98$), or health status outcomes. After intervention, participants of all ages had significant angina and health status improvement. Younger participants experienced a smaller decline in health status during follow-up than older participants (age by time interaction $p < 0.01$). The effect of the randomized glycemia treatment on clinical and health status outcomes was similar for patients of different ages.

Conclusions Among patients with stable heart disease and type 2 diabetes, the relative beneficial effects of a strategy of prompt revascularization versus initial medical therapy and insulin-sensitizing versus insulin-providing therapy on clinical endpoints, symptom relief, and perceived health status outcomes do not vary by age. Health status improved significantly after treatment for all ages, and this improvement was sustained longer among younger patients. (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes [BARI 2D]; NCT00006305) (J Am Coll Cardiol 2011;58:810–9) © 2011 by the American College of Cardiology Foundation

The effectiveness of coronary revascularization among older patients remains controversial. Concerns exist about higher procedural risk and lower long-term effectiveness in the elderly population (1). In previous randomized clinical trials comparing revascularization with medical therapy in patients with stable coronary heart disease, either treatment

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approach was shown to achieve a similar survival advantage for older and younger patients (2,3). However, in practice, older patients tend to receive less intensive treatment. Studies based on population registries found that patients with heart disease suitable for revascularization were less likely to undergo revascularization than younger patients (4,5). Another area of concern is that the prevalence of chronic conditions, such as heart disease, hypertension, and type 2 diabetes, increases with age (6). As most treatment protocols are designed to focus on a specific chronic condition, the optimal clinical approach to manage comorbidities simultaneously is not clear.

The BARI 2D (Bypass Angioplasty Revascularization Investigation Type 2 Diabetes) trial is a randomized clinical trial that evaluated the treatment strategies for patients with documented stable ischemic heart disease and type 2 diabetes. The main finding of the BARI 2D was that a treatment strategy of prompt revascularization or medical therapy for heart disease and a treatment strategy of insulin sensitization or insulin provision for type 2 diabetes resulted in similar rates of all-cause mortality and major cardiovascular events (7), whereas prompt revascularization was associated with modest improvement in angina relief and small but significant benefits in health status (8). Age was one of the pre-specified subgroup factors in the BARI 2D that might alter clinical outcomes. The present study investigated whether 1 treatment strategy would be especially advantageous for older patients and examined the primary hypothesis: whether the effectiveness of the randomized treatment strategies for ischemic heart disease differed by age. Treatment effectiveness was evaluated by clinical endpoints, symptom relief, and perceived health status outcomes.

Methods

Study settings. The study design, patient characteristics, and primary outcomes of the BARI 2D trial were published previously (9). In brief, 2,368 patients with angiographically documented stable ischemic heart disease and type 2 diabetes were randomized to receive 1 of the 2 ischemia treatments—prompt revascularization with intensive medical therapy or intensive medical therapy with delayed revascularization when necessary—and simultaneously randomized to one of the 2 glycemic treatments—insulin-sensitizing or insulin-providing drugs to target a hemoglobin A1c level lower than 7.0%. Before randomization, each consented patient was evaluated by a cardiologist to determine which revascularization strategy (coronary artery bypass graft or percutaneous coronary intervention [PCI]) was appropriate based on the extent of heart disease determined by coronary angiography and clinical factors. This intended revascularization strategy was the key stratification variable. Enrollment in the BARI 2D ran from January 1, 2001, to March 31, 2005. Study clinic visits occurred monthly for the first 6 months and every 3 months thereafter. When the trial follow-up ended on November 30, 2008, the 2,368 participants were followed for an average of 5.3 years.

Abbreviations and Acronyms

DASI = Duke Activity Status Index

PCI = percutaneous coronary intervention

Outcomes. CLINICAL ENDPOINTS. The clinical outcomes included death from all causes, major cardiovascular events (defined as the composite of death, myocardial infarction, and stroke), cardiac death, and subsequent revascularization procedures. Vital status was obtained from clinical visits supplemented with vital status sweeps performed annually. Diagnosis of myocardial infarction was based on serum cardiac biomarkers and core electrocardiography laboratory assessments. Stroke and cause of death were adjudicated by an independent committee.

Revascularization procedural complications included the occurrence of death and a composite of myocardial infarction and stroke within 30 days after the procedure, and adverse events that occurred during the index hospitalization.

ANGINA OUTCOMES. According to the BARI 2D protocol, angina was assessed at baseline and at every scheduled follow-up clinic visit. For the present study, we report the proportion of patients with angina during the past 6 weeks at the baseline visit and the proportion of surviving patients with angina reported during the previous year at each annual follow-up visit. Classic angina was defined as grades I to IV in the Canadian Cardiovascular Society Classification. Angina-equivalent symptoms were ischemic chest pain that resembled angina symptoms but were not classified as stable or unstable angina.

SUMMARY OF REPEATED HEALTH STATUS MEASURES. Health status was assessed at baseline and at each annual follow-up visit by 4 instruments: the Duke Activity Status Index (DASI) (10), the RAND Medical Outcome Study Energy/Fatigue Scale (11), RAND Health Distress (12), and self-rated health (13). DASI is a 12-item questionnaire that measures the functional capacity in patients with cardiac disease; the score ranges from 0 (worst) to 58.2 (best). The RAND Energy/Fatigue Scale (hereafter referred to as Energy) includes 5 items that evaluate how often in the past month that participants feel energetic or tired. To measure health distress, we adopted the appropriate items from the RAND batteries (modified RAND Health Distress [12], hereafter referred as Health Distress), evaluating how often the participant feels distressed about health. The Self-Rated Health score asks the participant to rate their health in general as excellent, very good, good, fair, or poor. We transformed the raw scores of the Energy, Health Distress, and Self-Rated Health to a 0 to 100 scale for comparison. Higher scores indicated more Energy, better self-rated health, but worse Health Distress. The health status measures have been validated in populations with different ages and chronic conditions (10,12,14) and are frequently used in randomized clinical trials for patients with cardiovascular diseases (15–17).

Statistical analysis. Baseline demographic, clinical, and health status profiles are summarized by 3 age groups (younger than 60 years, 60 to 69 years, or 70 years and older), and continuous variables were compared with Spearman rank correlation and categorical variables with a Mantel-Haenszel chi-square test for trend. The Fisher exact test was used in age comparisons of revascularization complications for rare events.

Kaplan-Meier survival analysis with log-rank test statistics was used to compare survival by baseline age groups, censored at 5 years of follow-up. We compared survival curves by randomized treatment assignments within each age subgroup and tested for an interaction between randomized treatment and baseline age group on clinical outcomes. We estimated the hazard ratio of adverse clinical outcomes associated with increasing age by Cox proportional hazards regression models. The proportional hazard assumption for the Cox models was tested, and nonproportional hazards were managed by stratification (18).

For the longitudinal analysis of health status, we truncated data at year 4 because an increasing proportion of patients did not have a year 5 clinical visit due to late enrollment. The occurrence of classic angina and angina equivalents at baseline and at each follow-up year was presented by age groups. We used generalized estimating equations to model the odds of angina at each follow-up year (19). For health status outcomes, we used linear mixed models to obtain the averaged effect of age or treatment on health status, accounting for the correlation in repeated outcome measures within each participant (20,21). The modeling approaches are summarized in the supplementary appendix of the report.

Multivariate models for both survival and longitudinal analysis were constructed to adjust for trial design variables including randomized treatment, important baseline clinical factors, and reported potential confounders in the association between age and health outcomes, including sex and cardiovascular complications (22). Treatment effect was analyzed based on the intention-to-treat principle; the interactions between baseline age and randomized treatment, intended revascularization method, and follow-up time were tested in all multivariate models. For subgroup analyses and effect modification, a 2-sided alpha level of 0.01 was used to control multiple comparisons. We examined the linear assumption and model fit (20) (summarized in the Online Appendix). All analyses were performed using SAS version 9.0 (SAS Institute, Cary, North Carolina).

Results

Baseline characteristics. The mean age of the 2,368 enrolled participants at baseline was 62.4 years, with a maximum age of 89.8 years. Of the 2,368 BARI 2D patients, 514 (21.7%) were age 70 years or older, and 38 patients (1.6%) were 80 years or older. Patients younger than 60 years of age were more likely to be smokers and to have a higher body mass index and lower systolic blood pressure but higher diastolic blood pressure and higher prevalence of myocardial infarction, whereas patients older than 60 years of age had a greater prevalence of cardiovascular disease history, such as hypertension, congestive heart failure, and stroke, and more often had bypass surgery selected as the intended method of coronary revascularization (Table 1). Older patients entered the study with longer duration of diabetes and higher prevalence of hypoglycemic episodes and neuropathy. It is notable that patients older than 70 years of age had lower mean hemoglobin A_{1c} level (7.1%), which was close to the glycemic control target in the BARI 2D, than younger age groups. At baseline, older age groups were associated with a lower DASI, but higher Energy, Health Distress, and self-rated health scores.

Age and randomized ischemia treatments. CLINICAL OUTCOMES. Over an average of 5.3 years of follow-up, adverse event rates increased by older age for death ($p < 0.001$) and major cardiovascular events ($p < 0.001$), but not for cardiac death ($p = 0.31$) (Table 2). Among patients appropriate for PCI, those who were younger than 60 years of age had a higher rate of subsequent procedures ($p = 0.014$). In Cox regression analysis, the effect of the assigned prompt revascularization strategy on clinical outcomes did not differ by age. Although medical therapy was associated with lower mortality than prompt revascularization for patients between 60 and 69 years of age, the interaction between age and revascularization was not significant ($p = 0.99$). For patients 70 years of age or older, the effect of prompt revascularization did not significantly differ from that of medical therapy for any of the 5-year clinical event outcomes. Age did not interact with revascularization for major cardiovascular events ($p = 0.081$) (Fig. 1), cardiac death, or subsequent procedures (Table 2). The interactions between age and assigned treatment were nonsignificant overall and within each of the intended revascularization strata. For example, the significance of the interaction between age and revascularization for the mortality outcome was $p = 0.11$ in the coronary artery bypass graft stratum and $p = 0.28$ in PCI stratum.

All age groups had low rates of revascularization procedural complications. Patients 70 years or older who underwent bypass surgery experienced more cardiogenic shock or hypotension and more congestive heart failure or pulmonary edema during the index hospitalization compared with younger patient groups (Table 3).

Longitudinal angina outcomes. At baseline, classic angina was more common among younger patients than among older patients ($p < 0.001$). After treatment, angina was reduced significantly ($p < 0.001$), with a similar degree of reduction in all age groups (odds ratios for year 4 angina vs. baseline angina were between 0.18 and 0.26 for all age groups). Consequently, classic angina continued to be more common among younger patients than among older patients

Table 1 Baseline Characteristics by Age

	Age <60 Yrs (n = 939)	Age 60–69 Yrs (n = 915)	Age ≥70 Yrs (n = 514)	p Value*
Trial parameters				
CABG strata	26.8	37.3	33.1	0.0015
Early revascularization	51.0	49.1	48.2	0.28
Insulin sensitizing	51.8	47.8	50.6	0.46
Demographic characteristics				
Male	70.5	73.0	65.4	0.11
Race				<0.001
White	58.6	70.4	71.2	
Black	19.8	14.5	15.4	
Hispanic	15.9	10.9	9.3	
Other	5.8	4.2	4.1	
Region of world				0.026
United States	62.3	60.2	70.6	
Canada	15.5	14.5	14.4	
Mexico	4.5	3.7	1.8	
Brazil	15.0	17.8	10.1	
Czech Republic/Austria	2.7	3.7	3.1	
Current cigarette smoker	20.1	10.4	2.3	<0.001
Body mass index, kg/m^2	32.6 ± 6.6	31.4 ± 5.6	30.6 ± 5.0	<0.001
Sitting SBP, mm Hg	128.5 ± 19.9	133.3 ± 20.0	134.8 ± 19.5	<0.001
Sitting DBP, mm Hg	76.8 ± 11.4	74.7 ± 10.7	70.0 ± 10.6	<0.001
Cardiac clinical history				
Myocardial infarction	35.0	30.1	30.1	0.031
Angina category				<0.001
None/angina equivalent only	33.5	42.0	45.3	
Stable CCS1/CCS2	44.7	41.0	41.2	
Stable CCS3/CCS4/unstable	21.8	17.0	13.4	
No. of diseased myocardial region (≥50%)				0.046
0 or 1	36.1	31.0	32.9	
2	36.0	35.9	35.6	
3	27.8	33.2	31.5	
Left ventricular ejection fraction <50%	16.9	17.9	17.8	0.63
Hypertension	79.4	84.8	84.2	0.007
Congestive heart failure	4.8	7.6	8.2	0.0071
Stroke	6.3	11.6	12.7	<0.001
Noncoronary artery disease	19.6	26.4	26.5	<0.001
Chronic obstructive pulmonary disease	4.1	5.8	5.5	0.16
Previous PCI	19.9	19.2	19.8	0.94
Previous CABG	5.2	6.8	8.0	0.034
Diabetes characteristics				
Duration of diabetes, yrs	8.5 ± 7.5	11.2 ± 8.7	12.6 ± 9.7	<0.001
Hemoglobin A_{1c}	8.0 ± 1.8	7.6 ± 1.6	7.1 ± 1.2	<0.001
Currently taking insulin	28.6	28.2	25.9	0.31
Hypoglycemic episode	20.9	23.3	25.3	0.048
Neuropathy: clinical MNSI >2	44.7	52.3	57.0	<0.001
Health status				
DASI (0–58.2)	19.7 ± 14.2	19.2 ± 13.5	17.0 ± 11.8	0.018
Energy score (0–100)	48.7 ± 23.2	53.1 ± 23.0	53.2 ± 21.8	<0.001
Health distress score (0–100)	47.2 ± 25.4	37.5 ± 24.7	33.4 ± 23.2	<0.001
Self-rated health (0–100)	34.8 ± 22.0	39.9 ± 21.2	43.3 ± 20.9	<0.001

Values are % or mean ± SD. *Continuous variables with Spearman rank correlation and categorical variables with a Mantel-Haenszel chi-square test for trend.
CABG = coronary artery bypass graft; CCS = Canadian Cardiovascular Society; DASI = Duke Activity Status Index; DBP = diastolic blood pressure; MNSI = Michigan Neuropathy Screening Instrument; PCI = percutaneous coronary intervention; SBP = systolic blood pressure.

throughout follow-up ($p < 0.05$). In contrast, the prevalence of angina-equivalent symptoms was similar in all age groups at baseline. After treatment, the prevalence of angina-equivalent symptoms decreased to a similar extent in all age groups (odds ratios for year 4 vs. baseline were between 0.29 and 0.32), and consequently angina-

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Table 2 5-Year Event Rate by Baseline Age Groups and Randomized Cardiac Treatment

	Age <60 Yrs		Age 60–69 Yrs		Age ≥70 Yrs		p Value	
Clinical Endpoints	REV (n = 479)	MED (n = 460)	REV (n = 449)	MED (n = 466)	REV (n = 248)	MED (n = 266)	Age Trend*	Age and REV Interaction†
Death, %	6.7	9.2	14.6	9.6	16.5	22.6	<0.001	0.99
Death/MI/stroke, %	19.9	19.1	23.3	21.6	27.7	36.6	<0.001	0.081
Cardiac death, %	4.2	5.8	7.9	4.4	5.9	8.1	0.31	0.98
Subsequent procedure, % by stratum								
Among intended CABG patients (n = 763)	14.1	43.6	7.1	33.5	2.8	47.3	0.33	0.10
Among intended PCI patients (n = 1,605)	33.5	48.3	27.5	39.3	27.1	39.7	0.014	0.36

*p value for comparing survival curve across age categories. †p value for interaction obtained from Cox regression models controlled for geographic region, intended revascularization method, and baseline angina status.
MI = myocardial infarction; MED = medical therapy; REV = revascularization; other abbreviations as in Table 1.

equivalent symptoms were present to a similar degree among all age groups at follow-up.

Patients assigned to prompt revascularization were significantly less likely to have classic angina symptoms at the 1-year follow-up compared with those assigned to medical therapy. The observed treatment differences were larger and more significant in the younger patient groups (Fig. 2); however, the effect of prompt revascularization on classic angina at 1 year did not vary significantly by age group (interaction $p = 0.62$). Using longitudinal mixed models, prompt revascularization resulted in a greater relief of classic angina than medical therapy in all age groups over the follow-up period (revascularization vs. medical therapy, odds ratio: 0.63, $p < 0.001$ overall; 0.61, $p < 0.001$ for ages younger than 60 years; 0.60, $p < 0.001$ for ages 60 to 69 years; and 0.71, $p = 0.032$ for ages 70 years and older). Assignment to prompt revascularization also resulted in a lower occurrence of angina equivalents in all age groups (revascularization vs. medical therapy, odds ratio: 0.77, $p < 0.001$ overall; 0.74, $p = 0.009$ for ages younger than 60 years; 0.80, $p = 0.047$ for ages 60 to 69 years; and 0.77, $p = 0.076$ for ages 70 years and older). There was no significant interaction between age and randomized cardiac treatment for classic angina ($p = 0.98$) or for angina equivalents ($p = 0.86$).

Longitudinal health status outcomes. A total of 2,163 patients with at least 1 follow-up health status measurement were included in the longitudinal analysis for health status. All 4 health status measures improved significantly from baseline to year 1 across the age categories (Fig. 3). After the first year, however, all 4 health status measures worsened over subsequent follow-up, and the rate of decline for DASI, Energy, and Health Distress was significantly greater among older patients ($p < 0.01$) (Table 4). After 4 years of follow-up, functional activity status (DASI) was significantly better compared with baseline for patients younger than 60 years of age at entry but was significantly worse than baseline for patients age 70 years or older. Energy scores were significantly better at 4 years compared with baseline for patients younger than 70 years of age at study entry but not for patients 70 years of age or older. Health Distress and Self-Rated Health were better at 4 years than at baseline for all age groups (Fig. 3).

The effect of the assignment to prompt revascularization on health status did not differ by baseline age (Table 4); the significance of the interactions were $p = 0.56$ for DASI, $p = 0.87$ for Energy, $p = 0.11$ for Health Distress, and $p = 0.064$ for Self-Rated Health. Averaged over age and follow-up years, prompt revascularization was associated with a small but significant increase in DASI score, Energy, and Self-Rated Health in multivariate models (Table 4). There was no significant interaction between age and the intended method of revascularization on health status outcomes. In the multivariate models, older age was associated with a steeper decline for DASI, Energy, and Health Distress over time ($p < 0.01$) (Table 4); this age by time interaction is illustrated in Figure 4.

Age and randomized glycemic treatments. Clinical outcomes after randomization to the insulin-sensitizing and insulin-providing strategies were also similar in all age groups: the interaction p values were 0.44 for death, 0.67 for major cardiovascular death, 0.85 for cardiac death, and 0.72 for subsequent procedures. The effect of randomization to glycemic treatment on health status did not differ by age; the interaction p values were 0.13 for DASI, 0.19 for Energy, 0.11 for Health Distress, and 0.31 for self-rated health.

Discussion

Prompt revascularization versus initial medical therapy and insulin-sensitizing versus insulin-providing therapy resulted in similar clinical outcomes of death, major cardiovascular events, and cardiac death among younger patients and among older patients. Over 4 years of follow-up, prompt revascularization was associated with a 39% reduction in odds of classic angina for patients younger than 60 years of age at baseline, 40% for patients between 60 and 69 years of age, and 29% reduction for patients older than age 70 years compared with initial medical therapy. The improvements in health status associated with prompt revascularization were also independent of age. Overall, younger patients were able to maintain initial improvements in health status over the 4 years of follow-up, whereas

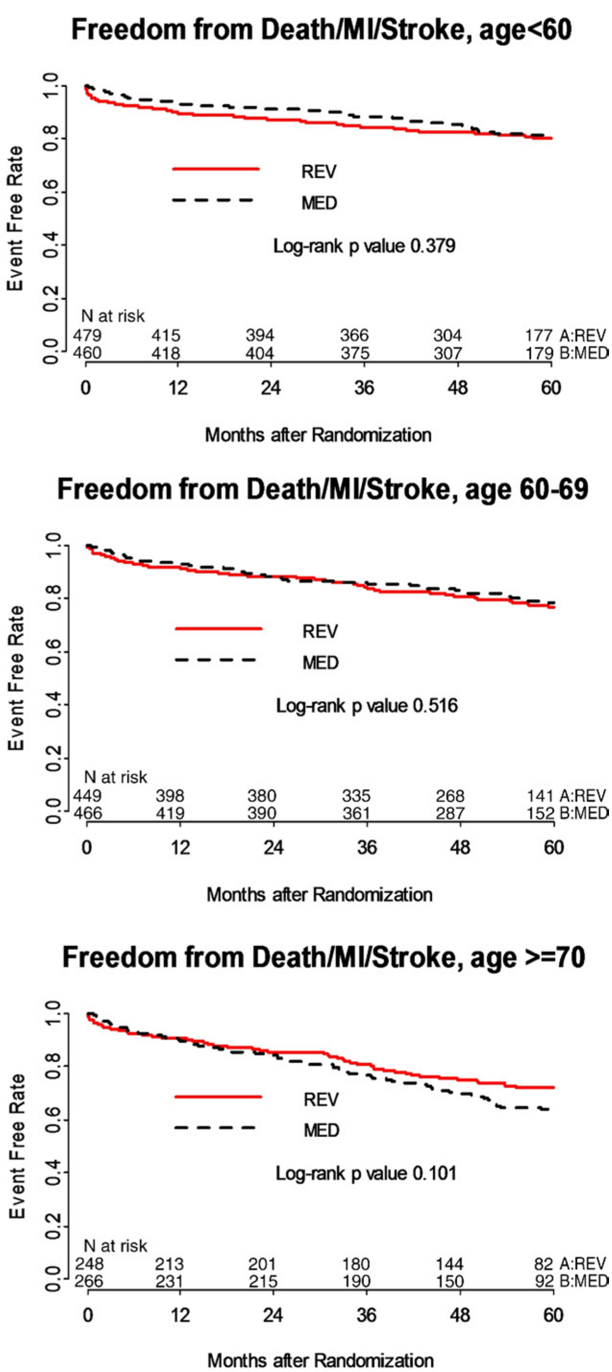

Figure 1 **Five-Year Survival Free of Major Cardiovascular Events**

Kaplan-Meier estimates comparing patients randomized to prompt revascularization (REV) **(solid red line)** versus medical therapy (MED) **(dashed black line)** stratified by baseline age category: age younger than 60 years, age 60 to 69 years, and age 70 years and older.

older patients experienced a decline in health status during follow-up. Therefore, although older patients have higher rates of death and major cardiovascular events than younger patients, the comparative treatment effectiveness of ischemia treatment strategies and glycemic control strategies, assessed by clinical outcomes, symptom relief, and health status, did not differ by age.

Previous randomized trials comparing revascularization with medical therapy for patients with stable ischemic heart disease have reported similar effects of revascularization for different age groups. In the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, in which 2,287 patients with stable coronary artery disease were randomized to receive either PCI or medical therapy, the effect of revascularization on mortality and other clinical outcomes did not differ by age groups (23). The CASS (Coronary Artery Surgery Study) reported similar outcomes with bypass surgery versus medical therapy for survival in various age groups of patients with stable angina (3). The European Coronary Surgery study reported a trend of greater survival benefit for bypass surgery over medical therapy in patients older than 53 years at baseline, but the effect modification between age and treatment was not statistically significant (24).

In the PROACTIVE (Prospective Pioglitazone Clinical Trial in Macrovascular Events) (25) and MICRO-HOPE (Heart Outcomes Prevention Evaluation) trials (26), which examined the effects of diabetes therapies and hypertension therapies, respectively, in patients with type 2 diabetes, there was no age difference in the effect of active treatment versus placebo on death and cardiovascular complications. To our knowledge, the present study is the first to simultaneously evaluate whether age modifies the effect of treatment strategies for stable coronary heart disease and for type 2 diabetes. Our findings showed similar clinical outcomes with prompt revascularization versus medical therapy and with insulin-sensitizing versus insulin-providing therapy for younger and older participants. The findings were consistent with those of previous clinical trials.

The complication rates for both revascularization procedures were very low in the BARI 2D. However, the study population is largely composed of middle-aged or young elderly individuals. Patients with left main coronary artery stenosis >50% or class III or IV heart failure were excluded. For patients receiving coronary artery bypass graft as their assigned revascularization procedure, a higher prevalence of procedural complications including congestive heart failure or pulmonary edema and cardiogenic shock or hypotension was observed in patients older than age 70 years at baseline. An inverse association between age and the subsequent procedure rate was observed in the present study as well as the original BARI trial (27). Potential reasons for this phenomenon may be that older patients were less willing to undergo another procedure or they had a greater tolerance of angina symptoms (28). Moreover, there may be some survival bias in that the sickest older patients were "censored" from the data for subsequent procedure analysis due to death.

Over the 4 years of follow-up, prompt revascularization was the preferable treatment strategy for relief of classic angina among older and younger patients. For patients with heart disease who were suitable for bypass surgery, revascu-

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Table 3 Revascularization Procedural Complications in Patients Randomized to Prompt Revascularization

	Age <60 Yrs	Age 60–69 Yrs	Age ≥70 Yrs	p Value*
CABG (n = 343)	n = 124	n = 148	n = 71	
Death	0.8	2.7	0	0.29
MI/stroke	3.2	3.4	4.2	0.86
CHF/pulmonary edema	0.8	0	2.8	0.055
Cardiogenic shock/hypotension	4.0	2.0	12.7	0.0049
Hemorrhage/bleeding†	1.6	5.4	5.6	0.20
Dementia/coma	0.0	2.0	4.2	0.067
Respiratory‡	3.2	4.1	7	0.49
Renal failure	1.6	0	0	0.17
Other	1.6	1.4	1.4	1.00
PCI (n = 752)	n = 323	n = 270	n = 159	
Death	0.6	0.7	0	0.83
MI/stroke	4.0	2.2	3.1	0.44
CHF/pulmonary edema	0.3	0	0	1.00
Cardiogenic shock/hypotension	1.6	1.5	1.3	1.00
Hemorrhage/bleeding	0.6	1.5	0	0.32
Renal failure	0.3	0	0	1.00
Other	0.3	1.1	2.5	0.091

Values are %. *Fisher exact test results. †Including hemorrhage requiring transfusion, reoperation for bleeding, or event other than hemorrhage requiring transfusion. ‡Contain respiratory failure including noncardiac pulmonary edema and adult respiratory distress syndrome; chest tubes left in place at least 3 days post-surgery.

CHF = congestive heart failure; other abbreviations as in Tables 1 and 2.

larization reduced the odds of classic angina by 58% compared with medical therapy. The effect of revascularization on angina-equivalent symptoms did not differ by age, indicating that revascularization was preferable for reducing atypical angina in patients of all ages.

Besides clinical endpoints and cardiac symptoms, this study evaluated how age and treatment affect patients' perceived health status over time. At baseline, older participants had lower functional capacity but higher perceived health status. After 1 year in the BARI 2D trial, the 4 health status measures improved significantly in every age group. Over subsequent follow-up, however, these initial gains eroded faster for older patients than for younger patients. Nevertheless, even the oldest patients improved compared with baseline in the levels of angina, Health Distress, and Self-Rated Health.

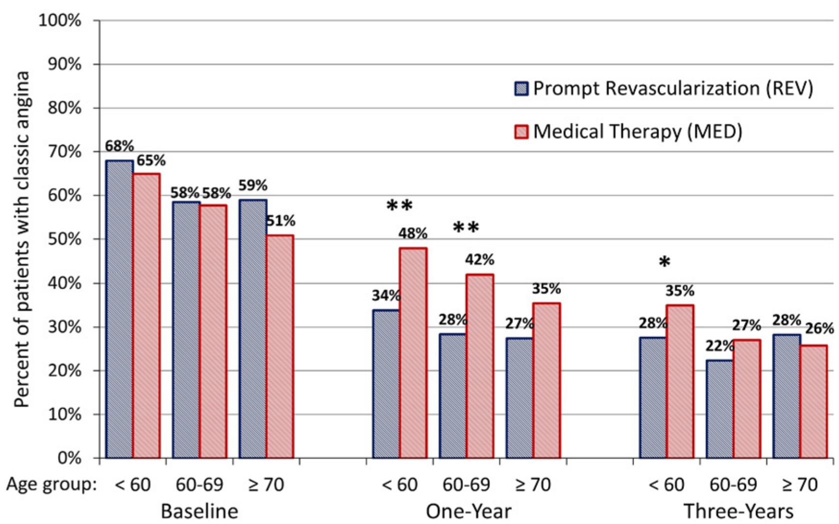

Figure 2 Classic Angina by Age Group and Randomized Treatment

The comparison of angina rates for patients randomized to REV **(blue bars)** versus MED **(red bars)** within age group at baseline, 1 year, and 3 years; statistical significance: *0.01 ≤ p < 0.05 and **p < 0.01. The significance of the interactions between age group and prompt revascularization is p = 0.40 at baseline, p = 0.62 at 1 year, and p = 0.23 at 3 years. Abbreviations as in Figure 1.

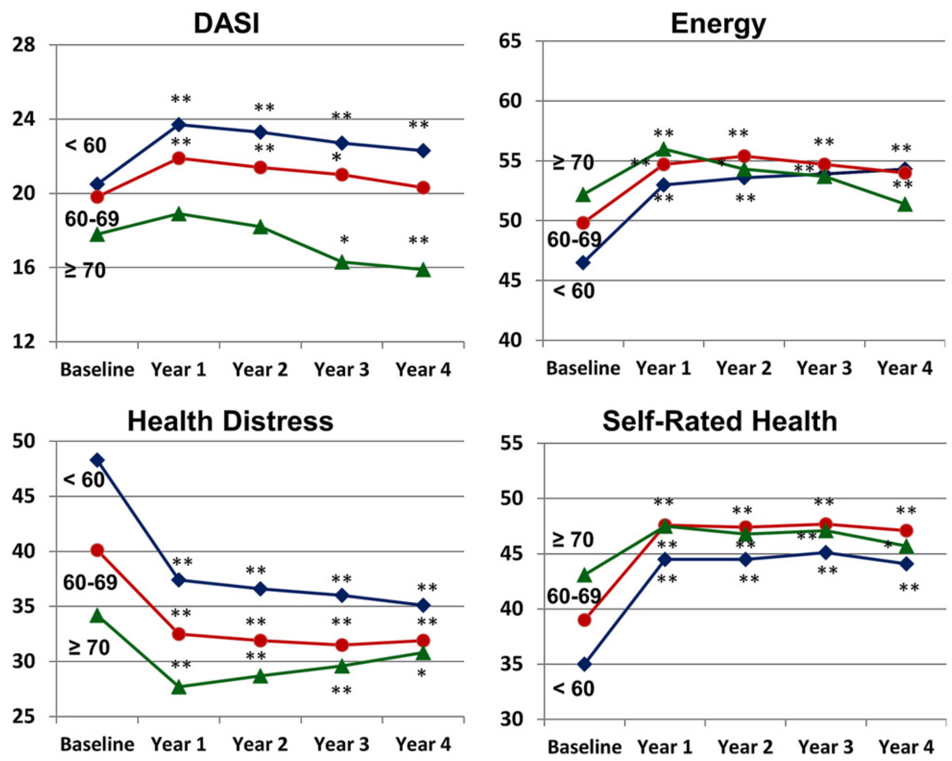

Figure 3 **Estimated Mean Health Status by Age Group and Time**

Estimates for Duke Activity Status Index (DASI), Energy, Health Distress, and Self-Rated Health are based on longitudinal mixed models accounting for baseline age group (younger than 60 years **[blue diamonds]**; 60 to 69 years **[red circles]**; 70 years and older **[green triangles]**), categorical follow-up time, the interaction between baseline age group and follow-up time, random site effect and missing data pattern. The estimated health status at each follow-up year is compared with baseline. Statistical significance: *0.01 ≤ p < 0.05 and **p < 0.01.

The association between age and health status has been assessed in a few randomized trials comparing revascularization and medical therapy. In the second Randomized Intervention Treatment of Angina study, the effect of age was independent of assignment to PCI or medical therapy (29). The TIME (Trial of Invasive Versus Medical Therapy in Elderly Patients With Chronic Symptomatic Coronary Artery Disease) compared the effect of revascularization versus medical therapy on health-related quality of life in 305 patients who were older than 75 and with chronic ischemic diseases. At 6 months of follow-up, the improvement in symptom relief and quality of life was greater for revascularization than for medical therapy (17), but the preferable results associated with revascularization disappeared at 1 year follow-up (1). In our trial, with an extended follow-up of 4 years, prompt revascularization treatment for heart disease resulted in a slightly greater health status im-

Table 4 **Health Status Outcomes During BARI 2D Follow-Up Based on Multivariable Regression Models***

Baseline Variables	DASI (0–58.2) Est	DASI p Value	Energy (0–100) Est	Energy p Value	Health Distress (0–100) Est	Health Distress p Value	Self-Rated Health (0–100) Est	Self-Rated Health p Value
Age at baseline (per 10 yrs)	−1.63	<0.001	0.13	0.75	−1.80	<0.001	−0.48	0.23
Follow-up time (per 1 yr)	−0.66	<0.001	−0.26	0.061	−0.16	0.34	−0.21	0.19
Age*: follow-up time interaction (per 10 yrs of age and 1 yr of follow-up)	−0.33	0.0015	−0.89	<0.001	0.91	<0.001		
REV vs. MED	1.24	0.0012	1.16	0.043	−0.36	0.59	1.72	0.0066
IS vs. IP	0.51	0.18	−0.31	0.58	−0.52	0.42	1.01	0.11
CABG stratum	0.61	0.18	1.60	0.018	−2.24	0.0038	3.08	<0.001
Baseline health status measure	0.51	<0.001	0.43	<0.001	0.41	<0.001	0.40	<0.001

*Model controlled for random site effect, and baseline variables including angina status, insulin use, sex, body mass index, smoking, history of hypertension, history of myocardial infarction, history of congestive heart failure, history of stroke, history of noncoronary artery disease, clinical evidence of neuropathy, missing data patterns.

BARI 2D = Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes; Est = Estimated Regression Coefficient; IP = insulin providing; IS = insulin sensitizing; other abbreviations as in Table 2.

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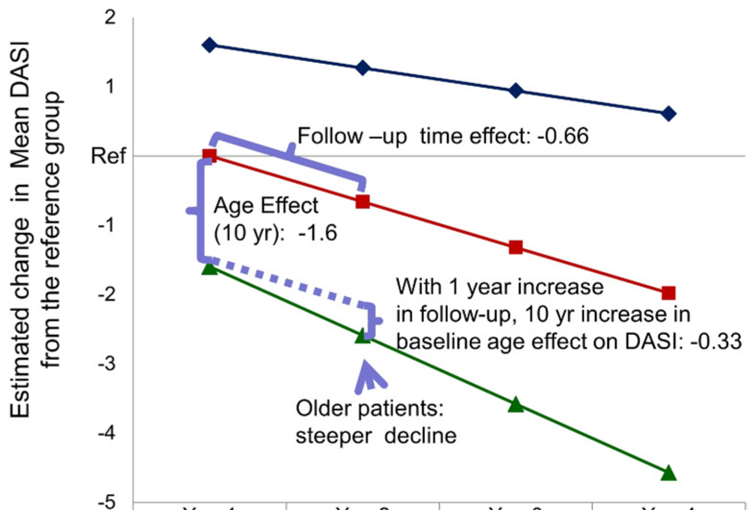

	Year1	Year2	Year3	Year4
10 yr younger (52.4)	1.6	1.27	0.94	0.61
Mean age (62.4)	Reference	-0.66	-1.32	-1.98
10 yr older (72.4)	-1.6	-2.59	-3.58	-4.57

Figure 4 **DASI by Baseline Age and Follow-Up Time**

Estimates and interpretation of the results from the Duke Activity Status Index (DASI) multivariate longitudinal mixed model that include an interaction between baseline age and follow-up time.

provement than medical therapy, and the beneficial effect is similar for older and younger patients.

Previous randomized trials for treatment of coronary artery disease have reported that health status changes start with a significant initial improvement from baseline and gradually wanes during follow-up years (25,30). We observed a similar trajectory. In addition, our study demonstrates that age modifies the changes in health status over time such that the decline in health status was greater in older than younger patients.

At baseline, greater angina severity was significantly associated with lower health status. The reduction in angina during follow-up may contribute to the overall improvement in participants' health status. It has been shown that among patients with similar health conditions, older individuals report better perceived health status than younger individuals (31). Likewise, we observed that older patients have better perceived health than younger patients, even with less capacity to perform daily tasks. Older participants in BARI 2D had lower body mass index, better diabetes control, and a lower proportion of current smoking and classic angina at baseline. The good disease self-management and lower classic angina prevalence in older participants may contribute to their better perceived health status. Because better self-rated health is associated with lower mortality in older individuals (32), it is possible that a positive attitude toward health contributes to the good condition of our elderly patients.

Study limitations. The BARI 2D included patients with moderate heart disease and type 2 diabetes suitable for either treatment strategy for ischemia management and glycemia control. Consequently, the study population might not fully represent all patients with heart disease and type 2 diabetes. Information on the occurrence of arthritis or dementia was not collected, which could contribute to the deterioration of health status. The longitudinal analysis was limited to patients with at least 1 follow-up health status measure, and patients without any follow-up health status information might be a concern. However, when we compared the results with those in sensitivity analyses in which missing health status outcomes were imputed using multiple imputations, the associations between age and health status outcomes were similar in the original and the expanded dataset. This suggests that the missing data did not substantially alter our study results. In addition to the quality data and study design in the BARI 2D, an additional strength of the present study was that older patients received revascularization according to treatment protocol. The underuse of invasive treatment strategies for older patients was minimized to enable the accurate investigation of treatment effect by age.

Conclusions

Among patients with documented stable heart disease and type 2 diabetes, the relative beneficial effects of a strategy of prompt revascularization versus initial medical therapy with delayed revascularization and insulin-sensitizing versus insulin-providing drug therapy on clinical endpoints, symptom relief, and perceived health status outcomes do not vary by age. Health status improved significantly after treatment for all ages, and this improvement was sustained longer among younger patients.

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Key Words: age ▪ coronary heart disease ▪ diabetes mellitus ▪ health status ▪ revascularization.

APPENDIX

For supplementary material, please see online version of this article.